

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61L 27/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/23090</b> <b>(43) International Publication Date:</b> 25 November 1993 (25.11.93)
<b>(21) International Application Number:</b> PCT/US93/04803 <b>(22) International Filing Date:</b> 20 May 1993 (20.05.93)  <b>(30) Priority data:</b> 4/127157                      20 May 1992 (20.05.92)                      JP  <b>(71) Applicant (for all designated States except US):</b> SHERWOOD MEDICAL COMPANY [US/US]; 1915 Olive Street, St. Louis, MO 63103-1642 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> OGAWA, Masaki [JP/JP]; 569-29, Kimune, Hamakita-City, Shizuoka Prefecture 434 (JP).  <b>(74) Agents:</b> SMITH, Montgomery W.; Sherwood Medical Company, 1915 Olive Street, St. Louis, MO 63103-1642 (US) et al.		<b>(81) Designated States:</b> AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ARTIFICIAL BLOOD VESSEL		
<b>(57) Abstract</b>  Artificial blood vessels having significantly improved anticlot characteristic and function, particularly for small-diameter artificial blood vessels. The artificial blood vessels, made of polyester, polyacrylonitrile or polyurethane, have their inner surfaces coated with 1 - 15 $\mu$ m thick, preferably 3 - 10 $\mu$ m thick, hydroxyapatite. The hydroxyapatite in the coating has a calcium atoms/phosphorus atoms ratio either in the range of 1 - 1.5, preferably 1.3 - 1.4, or in the range of 1.75 - 2.5, preferably 1.8 - 2.2.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

## Artificial Blood Vessel

### Technical Field

The present invention pertains to artificial blood vessels, more specifically to artificial blood vessels which  
5 have significantly improved anti-clot characteristic and function well as small-diameter artificial blood vessels.

### Background Art

Many patents on the artificial blood vessel have been applied and lively presentations and discussions have been  
10 continued at the conferences, etc. However, it is the artificial blood vessel of polyester fibers (Dacron) by DuPont woven in the tubular form and the artificial blood vessel of drawn out polytetrafluoroethylene that have been practically used in medical field.

15 These two share the market and use of other artificial blood vessels has been limited to exceptional circumstances or laboratory studies. Generally, for the large artificial vessels with diameters 8 - 36 mm, the use of the artificial blood vessel made of Dacron fabric is predominant, which has  
20 become a synonym for artificial blood vessel.

There are several methods of weaving fabrics used for artificial blood vessels, which are roughly divided into two types, namely, the plane weave and knit (meias). Blood  
25 leaks at the time of the transplantation and the seam must be closed with the blood itself or a fibrin glue. On the other hand, since pseudo intima is formed on the inner surface and it has a long-term advantage that it stabilizes with time. However, the formation of pseudo intima tends to decrease the inner radius and therefore it has not been  
30 widely used for small artificial blood vessels.

For the artificial blood vessel made of the drawn polytetrafluoroethylene, no initial blood leakage occurs, but it has a disadvantage that the pseudo intima does not develop on the inner surface as readily. Therefore, in the  
35 long run, it is inferior to the Dacron fabric artificial

blood vessel with respect to the biological compatibility including anti-clot characteristic. Nevertheless, it is often used for the artificial blood vessel with smaller diameters because the inner opening is more easily  
5 maintained because of the less pseudo intima.

Another unique example of artificial blood vessels was introduced in Science and Medical Applications of Hydroxyapatite, JAAS, 1991, pp. 185-189, TAKAYAMA Press System Center Co., Inc. However, this sintered  
10 hydroxyapatite is a brittle ceramic with extremely large elastic moduli and therefore its compliance is substantially different from that of actual blood vessel. Therefore it is valuable in laboratory study, but will not readily provide practical artificial blood vessels.

15 Disclosure of Invention

At present, for large artificial blood vessels with inner diameters greater than 8 mm, the artificial blood vessels available on the market pose no apparent difficulties. However, for small artificial blood vessels  
20 with 3 - 6 mm inner diameters, while many researches have been published, none of them have produced artificial blood vessels with satisfactory performance.

The primary reason for this is that there are the following two fundamental problems.

25 (a) Artificial blood vessels which have initially superior anti-clot characteristic at transplantation develop the pseudo intima slowly or does not develop it at all, thus the proportion of artificial blood vessels which remain open for a long period of time is small. On the other hand,  
30 artificial blood vessels which have poor initial anti-clot characteristic stabilize over a long period of time if the blockage does not occur at the beginning. However, the blockage often occurs due to the initial blood clotting and consequently, the proportion of artificial blood vessels  
35 which remain open is also small.

(b) The blockage often occurs due to the thickening of the intima at anastosis, which develops several months after transplantation.

The inventor of the present invention, after  
5 concentrated efforts to resolve these difficulties,  
discovered that (1) Hydroxyapatite adsorbs a large amount of  
albumin among proteins in the blood plasma. It is a common  
knowledge among researchers that the layer of albumin  
adsorption exhibits excellent anti-clot characteristic.  
10 (2) The less biologically compatible the artificial base  
material is, the more thickening of intima at anastomosis  
develops several months after transplantation.

On the basis of these discoveries, it is expected that  
hydroxyapatite which has proven excellent biological  
15 compatibility can be used for artificial blood vessels, and  
the use of hydroxyapatite for artificial blood vessels was  
introduced in the said literature. However, as previously  
described in the section of Existing Technology, when the  
artificial blood vessel is made of hydroxyapatite itself,  
20 such artificial blood vessel is not satisfactorily used in  
practice. The inventor therefore continued the research and  
developed the process of coating polymeric fabrics with  
hydroxyapatite, which lead to the present invention.

The methods for hydroxyapatite coating have been  
25 disclosed in many publications. Among them are: the  
sintering process in tokko Hei (1990) 13580; the plasma  
spray process for metallic implant materials in Tokko Sho 58  
(1983) -50737; the plasma jet process for ceramic core  
materials in Tokko Sho 59 (1984) - 46911, Tokkai Sho 62  
30 (1987) - 34539, Tokkai Sho 62 (1987) 57548, Tokkai Sho 63  
(1988) - 46165 and others; the sputtering process in Tokkai  
Sho 58 (1983) - 109049; the flame jet process in the  
Proceedings of the Japan Ceramics Society 1988 1st Fall  
Symposium, reprint, pp. 401-402; the glass frit baking  
35 process in The Proceedings of the 9th Conference of  
Miomaterials Society (reprint, 1987, p. 6); the

electrophoresis process in The Japan Ceramics Society, 1988, pp. 417-418; and the processes to precipitate hydroxyapatite from an artificial body fluid composed of ions of the same type and concentration as those in human blood plasma in  
5 Tokko Sho 61 (1986) - 10939, Tokko Hei 1 (1989) - 54290 and Tokkai Hei 2 (1990) -255515.

- As described above, various techniques for the hydroxyapatite coating have been published. Nevertheless, there remain many problems to be resolved, which include:
- 10 (a) The plasma jet process requires sophisticated and expensive equipment, and yet it does not readily produce fine coating and forms coating of apatite which is different from the apatite in the body because the source material, hydroxyapatite, is once melted at high temperatures.
  - 15 (b) The sputtering process requires sophisticated and expensive equipment and forms coating of apatite which is different from the apatite in the body because hydroxyapatite, the source material, is once melted at high temperatures. (c) The sintering and glass frit processes  
20 require heat treatments at temperatures 850°C or above and therefore can be applied only to base materials with high heat resistance and may form coating of apatite which is different from the apatite in the body because hydroxyapatite, the source material, is once treated at high  
25 temperatures.
  - (d) The electrophoresis process can be applied only to metallic base materials with good electric conductivity because it uses the base material itself as an electrode and also forms coating of apatite which is different from the  
30 apatite in vivo because it uses sintered apatite as the source material.
  - (e) The process of precipitating hydroxyapatite from an artificial body fluid has a handicap that no base materials, other than  $\text{CaO/SiO}_2$  base glass, which provide a good bonding  
35 with hydroxyapatite generated have been found.

As an example of the methods of (e) above, a process of coating polyester fabrics with hydroxyapatite has been published in Kinzoku (Metals), No. 12, 29-35 (1991). However, for hydroxyapatite having the calcium to phosphorus atomic ratio (Ca/P) close to its theoretical value 1.67, the bonding strength between such polyester fabric base material and the hydroxyapatite not sufficient and it is known that the bonding is easily separated under an external force and the corresponding strain. Therefore, it is obvious that it cannot be used for an artificial blood vessel in a living body where it is certainly subjected to repeated strains.

The present invention is intended to resolve the difficulties in the existing technology described above and to provide artificial blood vessels which have improved anti-clot characteristic and function well as small diameter artificial blood vessels.

In order to achieve the objective described above, the inventor improved the method of (e) and successfully developed the artificial blood vessel pertaining to the present invention.

That is, the artificial blood vessel developed in the present invention has the following features.

- (1) It is composed of the base material of polymeric fabric coated with 1  $15\mu\text{m}$  thick, preferably 3 -  $10\mu\text{m}$  thick, hydroxyapatite.
- (2) The range of Ca/P ratio of the said hydroxyapatite is 1.1 - 1.5, preferably 1.3 - 1.4.
- (3) Or the range of Ca/P ratio of the said hydroxyapatite is 1.75 - 2.5, preferably 1.8 - 2.2.
- (4) The said polymeric fabric is polyester, polyacrylonitrile or polyurethane, preferably polyester.
- (5) A part of the phosphate or hydroxyl group in the said hydroxyapatite has been substituted by carbonic group.

The reasons for limiting the base material for the artificial blood vessel in this invention to polymeric fabrics are that their mechanical properties (such as the

compliance) required for the artificial blood vessel have already been optimized, that they have been well proven to be safely used in the body, and that it is considered sensible to coat the base material or polymeric fabric with hydroxyapatite in order to provide practicable artificial blood vessels.

The reasons for coating the base material with hydroxyapatite are that the said coating adsorbs albumin in the blood on contact and exhibits an excellent anti-clot characteristic, and that its excellent biological compatibility effectively reduces the thickening of intima at the anastomosis.

The reasons for limiting the range of thickness of hydroxyapatite coating in the artificial blood vessels pertaining to the present invention to 1 - 15  $\mu\text{m}$ , preferably 3 - 10  $\mu\text{m}$ , are that, if the thickness is below 1  $\mu\text{m}$ , uniform coating is not reliably produced in practice and the hydroxyapatite may erode and disappear over a period of time after transplantation, and that, if the thickness exceeds 10  $\mu\text{m}$ , its flexibility decreases significantly.

In addition, in the present invention, the range of the Ca/P ratio is limited to either 1.1 - 1.5, preferably 1.3 - 1.4, or 1.75 - 2.5, preferably 1.8 - 2.2. This is based on the following. If this ratio is below 1.1, the peak for hydroxyapatite crystal in the thin film X-ray diffraction almost disappears. If it ranges from 1.5 to 1.75, microcracks initiate in the coating formed, which readily lead to separation under cyclic strains encountered in practice. Also, if it exceeds 2.5, the peak for hydroxyapatite crystal in the thin film X-ray diffraction virtually disappears as well.

These behaviors may be reasoned as follows. The Ca/P ratio in hydroxyapatite is theoretically 1.67, whereas this ratio in actual living body is said to be about 1.5. The Ca/P ratio in the coating formed in the present invention deviated from the theoretical value promotes formation of



calcium phosphate in the microcrystalline or amorphous form in addition to hydroxyapatite, thus preventing crack initiation.

The presence of such microcracks greatly affects the bonding strength between polymeric fabric constituting the base material and hydroxyapatite, namely, significantly decreases the bonding strength and the flexibility.

In addition, it was discovered that, when this ratio is shifted to a value greater than 1.67, that is that in the range of 1.7 - 2.5, the bonding strength between the polymeric fabric base material and hydroxyapatite coating formed, surprisingly, increases substantially. This fact had not been known at all previously.

In the present invention, the preferred polymeric fabrics used for the base material is polyester, polyacrylonitrile or polyurethane. Polyester is particularly preferred because the polyester base artificial blood vessel has been successfully used and is more reliable.

The preferable hydroxyapatite in the present invention is that with a part of its phosphate or hydroxyl group substituted by carbonic group, because in such form it is closer to hydroxyapatite in a living body and has better biological compatibility.

#### Best Modes for Carrying Out the Invention

The artificial blood vessel in the present invention is prepared as follows. The artificial blood vessel with inner diameter 6 mm made of polyester fabric USCI DeBaKey P-005106 manufactured by Bird Co. is used for the base material and the glass powder, which has grain diameters 100 - 600 $\mu$ m and the composition presented in Tokkai Hei 2 (1990) -25515, is filled in the said artificial blood vessel.

The ranges of CaO and SiO<sup>2</sup> compositions in the said glass are

CaO .....20 - 60 mol%

$\text{SiO}_2$  .....40 - 80 mol%

and the composition of  $\text{CaO}$  and  $\text{SiO}_2$  combined is at least 70 mol%. More than 80% of the glass powder has grain diameters 100 - 600 $\mu\text{m}$ .

5 The composition of the said glass is as follows.

$\text{CaO}$  .....49.87 mol%

$\text{SiO}_2$ ..... 35.46

$\text{P}_2\text{O}_5$ ..... 7.153

$\text{MgO}$  ..... 7.111

10  $\text{CaF}_2$ ..... 0.399

The artificial blood vessel filled with the glass powder was immersed in an artificial body fluid A practically supersaturated with hydroxyapatite for 48 hours. The compositions of the artificial body fluids A and B are  
15 as follows.

	Artificial Body Fluid	Artificial Body Fluid
	A	B
	$\text{NaCl}$ 7.996 g	11.994 g
	$\text{NaHCO}_3$ 0.350	0.525
20	$\text{KCl}$ 0.224	0.336
	$\text{K}_2\text{HPO}_4 \cdot 3\text{H}_2\text{O}$ 0.228	0.342
	$\text{MgCl}$ 0.305	0.458
	$\text{CaCl}_2$ 0.278	0.417
	$\text{Na}_2\text{SO}_4$ 0.071	0.107
25	1N $\text{HCl}$ approx. 45 ml	approx. 68 ml
	Tris(hydroxymethyl) aminomethane 6.057	8.086

A-carbonate  $\text{NaHCO}_3$  is included in these artificial body fluids. It has been verified that the hydroxyapatite layer  
30 formed from such artificial body fluids has a part of its phosphate group or hydroxyl group substituted by carbonic group. Hydroxyapatite in a living body is also known to have carbonic group replacing a part of its phosphate group or hydroxyl group.

After the artificial blood vessel was immersed in the artificial body fluid for 48 hours, the glass powder was removed from the artificial blood vessel and the inside was cleaned. Then the artificial blood vessel was immersed in  
5 the artificial body fluid B for 1 week. This artificial blood vessel was removed from the artificial body fluid, rinsed with water and dried. Then it was sterilized by ethylene oxide gas in a sterilizing bag.

The thickness of hydroxyapatite coating was controlled  
10 by changing the duration of immersion in the artificial body fluid. Tables I and II summarize the results of the experiments described above for artificial blood vessels pertaining to the present invention, with various thicknesses of hydroxyapatite coating.

TABLE I

	Experiments						
	1	2	3	4	5	6	7
Thickness of Coating ( $\mu\text{m}$ )	--	0.8	1.5	3.8	9.2	15	18
Presence of Cracking	--	no cracks	no cracks	no cracks	no cracks	no cracks	no cracks
Ca/P Ratio	--	1.8	1.8	1.8	1.8	1.8	1.8
Flexibility	--	no problem	no problem	no problem	micro-cracks	cracks observed	partially separated
Anti-Clot Characteristic							
after 1 month	moderate clotting observed	moderate clotting observed	a little clotting observed	no clotting			not tested
after 3 months	a little clotting observed	a little clotting observed	no clotting	no clotting			
after 6 months	no clotting	no clotting	no clotting	no clotting			
Thickening at Anasomosis							
after 3 months	moderate	moderate	minor		none		not tested
after 6 months	severe	severe	minor		none		

TABLE II

	Experiments						
	8	9	10	11	12	13	14
Thickness of Coating ( $\mu\text{m}$ )	10	10	10	10	10	9.5	10
Presence of Cracking	no cracks	no cracks	no cracks	no cracks	cracks observed	large cracks	no cracks
Ca/P Ratio	1.0	1.1	1.3	1.5	1.6	1.65	1.8
Flexibility	micro-cracks	micro-cracks	micro-cracks	micro-cracks	a little partially separated	a little partially separated	no problem
Anti-Clot Characteristic							
after 1 month	moderate clotting observed	a little clotting observed	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
after 3 months	a little clotting observed	no clotting	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
after 6 months	no clotting	no clotting	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
Thick ning at Anasomosis							
after 3 months	minor	minor	none	none	none	none	none
after 6 months	severe	severe	minor	none	none	none	none

The Ca/P ratio in hydroxyapatite was controlled by adjusting the ratio of dipotassium hydrogenphosphate/calcium chloride and the hydrogen ion concentration in the artificial body fluid.

5       The observation of the thickness of hydroxyapatite coating and the cracking were made by a scanning electron microscope. The Ca/P ratio was measured by a polymer microanalyzer.

10       The tube fatigue tests were performed as follows. The artificial blood vessel coated with hydroxyapatite was fixed inside an elastomer tube with the inner diameter 7.6 mm and the length 150 mm and this tube was placed around a pulley so that it was subjected to repeated 90° bending. After fatigue loading by rotating the pulley at 200 r.p.m. for 30  
15 minutes, the presence of separation and cracking of the coating was examined by a scanning electron microscope to evaluate the flexibility.

20       In addition, about 20 mm of pulmonary arteries of grown dogs were replaced by artificial blood vessels, which were removed and observed after 1 month, 2 months and 6 months to evaluate the anti-clot characteristic and thickening at anasomosis.

25       The features of the artificial blood vessel pertaining to the present invention described above made it possible to provide the artificial blood vessels which have much superior anti-clot characteristic and function well as a small-diameter artificial blood vessels.

Claims

1. An artificial blood vessel characterized in that said blood vessel includes a base material made of a polymeric fabric and a 1 - 15 $\mu$ m thick coating of  
5 hydroxyapatite.
2. The artificial blood vessel described in Claim 1 further characterized in that said coating of hydroxyapatite is 3 - 10 $\mu$ m thick.
3. The artificial blood vessel described in Claims 1 or  
10 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.1 - 1.5
4. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.3 - 1.4.
- 15 5. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.75 - 2.5.
6. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said  
20 hydroxyapatite is in the range of 1.8 - 2.2.
7. The artificial blood vessel described in Claims 1, 2, 3, 4, 5 or 6 characterized in that said polymeric fabric material is polyester, polyacrylonitrile or polyurethane.
8. The artificial blood vessel described in Claims 1,  
25 2, 3, 4, 5, 6 or 7 characterized in that a part of a phosphate group or a hydroxyl group in said hydroxyapatite has been substituted by a carbonic group.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/04803

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>Int.Cl. 5 A61L27/00</b>														
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border: 1px solid black; padding: 2px; margin: 5px 0;">Minimum Documentation Searched<sup>7</sup></div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; padding: 5px;">Classification System</th> <th style="padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">Int.Cl. 5</td> <td style="padding: 5px;">A61L</td> </tr> </table> <div style="text-align: center; border: 1px solid black; padding: 2px; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched<sup>8</sup></div>			Classification System	Classification Symbols	Int.Cl. 5	A61L								
Classification System	Classification Symbols													
Int.Cl. 5	A61L													
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category<sup>10</sup></th> <th style="padding: 5px;">Citation of Document,<sup>11</sup> with indication, where appropriate, of the relevant passages<sup>12</sup></th> <th style="width: 10%; padding: 5px;">Relevant to Claim No.<sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;"> <b>EP,A,0 389 713 (KYOTO UNIVERSITY)</b>  <b>3 October 1990</b>  <b>see page 6, line 41 - line 42</b>  <b>see page 7, line 24</b>  <div style="text-align: center;">---</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;"> <b>EP,A,0 437 975 (SUMITOMO)</b>  <b>24 July 1991</b>  <b>see column 4, line 43 - line 49; claims 4,7</b>  <div style="text-align: center;">---</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1,3-6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,A</td> <td style="padding: 5px;"> <b>WO,A,9 307 916 (SHERWOOD MEDICAL)</b>  <b>29 April 1993</b>  <b>see page 9, line 1 - line 8; claims 1,2,12</b>  <div style="text-align: center;">---</div> <div style="text-align: right; margin-top: 10px;">-/--</div> </td> <td style="text-align: center; vertical-align: top; padding: 5px;">1</td> </tr> </tbody> </table>			Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	A	<b>EP,A,0 389 713 (KYOTO UNIVERSITY)</b> <b>3 October 1990</b> <b>see page 6, line 41 - line 42</b> <b>see page 7, line 24</b> <div style="text-align: center;">---</div>	1	A	<b>EP,A,0 437 975 (SUMITOMO)</b> <b>24 July 1991</b> <b>see column 4, line 43 - line 49; claims 4,7</b> <div style="text-align: center;">---</div>	1,3-6	P,A	<b>WO,A,9 307 916 (SHERWOOD MEDICAL)</b> <b>29 April 1993</b> <b>see page 9, line 1 - line 8; claims 1,2,12</b> <div style="text-align: center;">---</div> <div style="text-align: right; margin-top: 10px;">-/--</div>	1
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>												
A	<b>EP,A,0 389 713 (KYOTO UNIVERSITY)</b> <b>3 October 1990</b> <b>see page 6, line 41 - line 42</b> <b>see page 7, line 24</b> <div style="text-align: center;">---</div>	1												
A	<b>EP,A,0 437 975 (SUMITOMO)</b> <b>24 July 1991</b> <b>see column 4, line 43 - line 49; claims 4,7</b> <div style="text-align: center;">---</div>	1,3-6												
P,A	<b>WO,A,9 307 916 (SHERWOOD MEDICAL)</b> <b>29 April 1993</b> <b>see page 9, line 1 - line 8; claims 1,2,12</b> <div style="text-align: center;">---</div> <div style="text-align: right; margin-top: 10px;">-/--</div>	1												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents : <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>														
<b>IV. CERTIFICATION</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> <b>Date of the Actual Completion of the International Search</b>  <div style="text-align: center; font-weight: bold; margin-top: 10px;">24 AUGUST 1993</div> </td> <td style="width: 50%; padding: 5px;"> <b>Date of Mailing of this International Search Report</b>  <div style="text-align: center; font-weight: bold; margin-top: 10px;">06. 09. 93</div> </td> </tr> <tr> <td style="padding: 5px;"> <b>International Searching Authority</b>  <div style="text-align: center; font-weight: bold; margin-top: 10px;">EUROPEAN PATENT OFFICE</div> </td> <td style="padding: 5px;"> <b>Signature of Authorized Officer</b>  <div style="text-align: center; font-weight: bold; margin-top: 10px;">PELTRE CHR.</div> </td> </tr> </table>			<b>Date of the Actual Completion of the International Search</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">24 AUGUST 1993</div>	<b>Date of Mailing of this International Search Report</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">06. 09. 93</div>	<b>International Searching Authority</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">EUROPEAN PATENT OFFICE</div>	<b>Signature of Authorized Officer</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">PELTRE CHR.</div>								
<b>Date of the Actual Completion of the International Search</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">24 AUGUST 1993</div>	<b>Date of Mailing of this International Search Report</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">06. 09. 93</div>													
<b>International Searching Authority</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">EUROPEAN PATENT OFFICE</div>	<b>Signature of Authorized Officer</b> <div style="text-align: center; font-weight: bold; margin-top: 10px;">PELTRE CHR.</div>													



## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	<p>DATABASE WPIL Week 8631, Derwent Publications Ltd., London, GB; AN 86-202289 &amp; JP,A,61 135 670 (MITSUBISHI) see abstract -----</p>	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9304803  
SA 74471

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

24/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0389713	03-10-90	JP-A- 2255515 US-A- 5068122	16-10-90 26-11-91
EP-A-0437975	24-07-91	JP-A- 3207369 US-A- 5128169	10-09-91 07-07-92
WO-A-9307916	29-04-93	JP-A- 5103827	27-04-93